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# Nickel-catalyzed Chan–Lam coupling: an efficient route to *N*-arylated 2-aminobenzothiazoles under ambient conditions

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A nickel-catalyzed C–N coupling of 2-aminobenzothiazoles and aryl boronic acids under mild reaction conditions is disclosed. The reaction afforded *N*-arylated 2-aminobenzothiazoles in the presence of a Ni/4,4′-dOMebpy catalytic system under open-air conditions. The method encompasses a wide range of applicable substrates, including aryl boronic acids and 2-aminobenzothiazoles, affording the corresponding C–N coupled products in moderate to good yields in short reaction times.



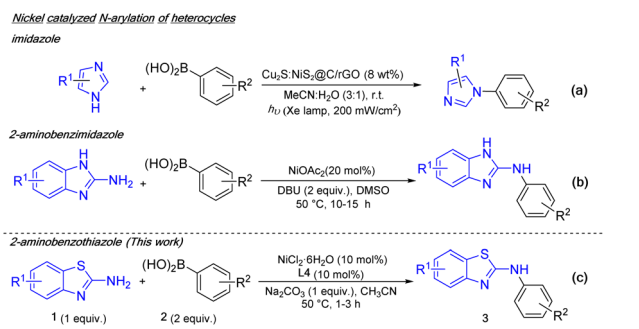
## Introduction

The construction of C–N bonds is a highly active area of research as C–N bonds are omnipresent in biochemical structures and natural products.[1,2] Transition metal-catalyzed C–N bond-forming reactions have emerged as powerful tools, offering greater efficiency in synthesising aryl/heteroaryl compounds possessing nitrogenous functional groups.[3] The conventional C–N bond formation through electrophile-nucleophile coupling is demonstrated by Ullmann–Goldberg reactions[4] and Buchwald–Hartwig aminations.[5] The Ullmann–Goldberg and Buchwald–Hartwig reactions refer to the Cu-mediated and Pd-catalyzed arylation of amines using aryl(-pseudo)halides, respectively, to render arylamines.[6] While extensive investigations have been made, Ullmann–Goldberg or Buchwald–Hartwig aminations pose certain limitations including the need of elevated temperatures, expensive Pd (pre) catalysts and strong bases to achieve optimal results.[7] In 1998, Chan, Lam and Evans independently reported that copper salts facilitate the oxidative coupling of arylboronic acids with *N*- and *O*-nucleophiles to render C–X coupled products.[8] The defining feature of this new Chan–Lam cross-coupling is the simple reaction conditions including inexpensive reagents, room temperature conditions, use of a weak base, and the "open-flask" chemistry.[9]

From the initial report of Raghuvanshi *et al.*,[10] Ni-based catalysts emerged as a viable alternative to Cu-catalysed Chan–Lam reactions to achieve efficient C–N and C–S cross-couplings. Nickel, being a low-cost and earth-abundant metal with proven catalytic activity, has garnered significant attention in organic synthesis.[11] Although considerably less studied than Cu-catalysed Chan–Lam reactions, continual progress has also been made on the Ni-catalyzed version with respect to the use of novel Ni complexes, newer substrates and chemo-, regio- and enantioselective variants.[12]

Over the past years, Chan–Lam coupling has also found utility in the arylation of NH-heterocycles for synthesizing functionalized aryl heterocycles of interest.[1] Similar Ni-catalyzed transformations have been studied in recent years, where *N*-arylation of imidazoles,[13] pyroglutamates,[14] chemoselective *N*-arylation of 2-aminobenzimidazoles,[15] *etc.* were successfully demonstrated (Scheme 1, paths a & b). To further expand the scope, we achieved the *N*-arylation of 2-aminobenzothiazole, a privileged class of fused heterocycles.

2-Aminobenzothiazole constitutes a fused bicyclic framework with diverse medicinal and agrochemical applications.[16] These scaffolds gained much attention because of their bioactivities including anti-inflammatory,[17] antiviral,[18] anticancer,[19] antidiabetic,[20] antimalarial,[21] antidepressant,[22] and so on. Importantly, heterocyclic scaffolds hold a crucial role in drug design,[23] and there exist a series of *N*- and *S*- containing FDA-




Scheme 1 Previous Ni-catalyzed strategies (a and b) and the present work (c) for the synthesis of functionalized heterocycles *via* Chan–Lam coupling.

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approved drugs so far.[24] Given the importance, numerous protocols towards the synthesis and functionalization of 2-aminobenzothiazoles are still in demand.

As part of our continuing interests in low-cost transition metal catalysed cross-couplings and heterocycle synthesis,[25] we envisioned the potential applicability of Ni-catalyzed Chan–Lam coupling in the *N*-arylation of 2-aminobenzothiazoles. Herein, we present a facile synthesis of *N*-arylated 2-aminobenzothiazole derivatives *via* Chan–Lam coupling of 2-aminobenzothiazoles and phenyl boronic acids under Ni catalysis. The optimal reaction employed Ni/4,4′-dOMebpy catalytic system in the presence of $Na_2CO_3$ as the base in acetonitrile at 50 °C for 1–3 h reaction time (Scheme 1, path c). This reaction could be effectively carried out under air without the need for any external oxidant.

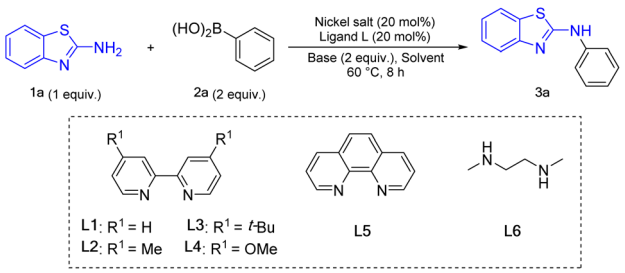
## Results and discussion

In the initial studies, 2-aminobenzothiazole **1a** and phenyl boronic acid **2a** were chosen as model substrates for the reaction. Based on the previously known Ni-based catalytic systems in Chan–Lam coupling,[9] we have identified $NiCl_2 \cdot 6H_2O$ (20 mol%) as the catalyst along with 2,2′-bipyridine (20 mol%) as the ligand in the presence of $Na_2CO_3$ (2 equiv.) as the base in acetonitrile for the coupling reaction between **1a** and **2a**. The reaction mixture was stirred in an open vessel at 60 °C for 8 h. Under this condition, the reaction afforded the desired C–N coupled product *N*-phenylbenzo[*d*]thiazol-2-amine **3a** in 55% yield. The structure of the column-purified product was confirmed by HRMS and NMR analyses. From the GC-MS analysis, the reaction mixture showed phenol and biphenyl as the byproducts derived from phenyl boronic acid upon oxidation and reductive homocoupling, respectively. This accounted for the reduction in the conversion of **1a** in the reaction.

An extensive optimization study was performed to arrive at the best reaction condition for this transformation, minimizing the possible byproducts. Changing the Ni source from $NiCl_2 \cdot 6H_2O$ to other nickel salts did not improve the reaction yields (Table 1, entries 1–5). Additionally, the necessity of nickel catalyst was verified experimentally, and the expected product did not form in the absence of $NiCl_2 \cdot 6H_2O$ (Table 1, entry 6). While screening ligands, bipyridine ligands **L1–L4** proved effective, consistent with the literature-known Ni-catalyzed Chan–Lam coupling reactions[9] (Table 1, entries 7–9). Among these, 4,4′-dimethoxy-2,2′-bipyridine **L4** provided the highest yield of 71%, making it a promising candidate (Table 1, entry 9). Bidentate *N*-donor ligands like 1,10-phenanthroline and diamines resulted in lower yields (Table 1, entries 10,11). The *O*-donor ligands such as 1,1′-bi-2-naphthol and *trans*-1,2-cyclohexanediol, and a ligand-free reaction afforded only traces of the product (SI, Table 3.2).

Subsequently, a range of bases, including inorganic and organic bases, were screened (SI, Table 3.3). $Na_2CO_3$ proved to be the optimal base, yielding 71% of the product, whereas other inorganic bases cannot improve the yields (Table 1, entries 13,14). Further exploration of organic bases revealed that bases like DABCO and $Et_3N$ rendered 57% and 47% of the product, respectively, while DBU only provided traces of the product in this reaction (SI, Table 3.3). Under base-free conditions, the formation of **3a** was lowered to 48% yield (Table 1, entry 16).

Table 1 Optimization studies for the Ni-catalysed C–N coupling of 2-aminobenzothiazole **1a** and phenyl boronic acid **2a**[a]




| Entry | Ni catalyst | Ligand | Base | Solvent | Yield (%)[b] |
|---|---|---|---|---|---|
| 1 | $NiCl_2 \cdot 6H_2O$ | **L1** | $Na_2CO_3$ | $CH_3CN$ | 55 |
| 2 | $Ni(OAc)_2 \cdot 4H_2O$ | **L1** | $Na_2CO_3$ | $CH_3CN$ | 39 |
| 3 | $Ni(NO_3)_2 \cdot 6H_2O$ | **L1** | $Na_2CO_3$ | $CH_3CN$ | 49 |
| 4 | $NiBr_2$ | **L1** | $Na_2CO_3$ | $CH_3CN$ | 34 |
| 5 | $Ni(acac)_2$ | **L1** | $Na_2CO_3$ | $CH_3CN$ | 33 |
| 6 | — | **L1** | $Na_2CO_3$ | $CH_3CN$ | nr |
| 7 | $NiCl_2 \cdot 6H_2O$ | **L2** | $Na_2CO_3$ | $CH_3CN$ | 65 |
| 8 | $NiCl_2 \cdot 6H_2O$ | **L3** | $Na_2CO_3$ | $CH_3CN$ | 57 |
| **9** | **$NiCl_2 \cdot 6H_2O$** | **L4** | **$Na_2CO_3$** | **$CH_3CN$** | **71** |
| 10 | $NiCl_2 \cdot 6H_2O$ | **L5** | $Na_2CO_3$ | $CH_3CN$ | 43 |
| 11 | $NiCl_2 \cdot 6H_2O$ | **L6** | $Na_2CO_3$ | $CH_3CN$ | 43 |
| 12 | $NiCl_2 \cdot 6H_2O$ | — | $Na_2CO_3$ | $CH_3CN$ | traces |
| 13 | $NiCl_2 \cdot 6H_2O$ | **L4** | $K_2CO_3$ | $CH_3CN$ | 66 |
| 14 | $NiCl_2 \cdot 6H_2O$ | **L4** | NaOH | $CH_3CN$ | 41 |
| 15 | $NiCl_2 \cdot 6H_2O$ | **L4** | $Et_3N$ | $CH_3CN$ | 47 |
| 16 | $NiCl_2 \cdot 6H_2O$ | **L4** | — | $CH_3CN$ | 48 |
| 17 | $NiCl_2 \cdot 6H_2O$ | **L4** | $Na_2CO_3$ | DMSO | 34 |
| 18 | $NiCl_2 \cdot 6H_2O$ | **L4** | $Na_2CO_3$ | DMF | 46 |
| 19 | $NiCl_2 \cdot 6H_2O$ | **L4** | $Na_2CO_3$ | DCE | 57 |
| 20 | $NiCl_2 \cdot 6H_2O$ | **L4** | $Na_2CO_3$ | EtOH | 38 |

[a] Reaction conditions: **1a** (0.3 mmol), **2a** (0.6 mmol), Nickel salt (20 mol%), ligand (20 mol%), base (2 equiv.), solvent (2 mL), 8 h, 60 °C. [b] Isolated yield.

Analysis of the most widely used polar aprotic solvents revealed that $CH_3CN$ is the most suitable solvent that rendered maximum yield, while DMSO, DMF and DCE gave moderate yields of the product (SI, Table 3.4). Other screened polar protic solvents lead to lower conversion of starting materials, accompanied with inferior yields (SI, Table 3.4). Encouragingly, the reaction proceeded smoothly with similar yields at a reduced temperature of 50 °C (Table 2, entry 3). A reaction at room temperature and at 70 °C didn't improve the reaction yields (Table 2, entry 2; SI, Table 3.5). Then, the reaction time was varied at the optimal temperature of 50 °C.

It is noteworthy that the reaction offered comparable yields even at a shortened period of 4 h and 1 h, suggesting faster reaction rates (Table 2, entries 5,6). Upon altering the catalyst loadings, we found that 10 mol% of $NiCl_2 \cdot 6H_2O$ and **L4** was sufficient for the formation of **3a** in good yields (Table 2, entry 7). Further attempts to reduce the catalyst loading to 5 mol% resulted in lowered yield of 65% (Table 2, entry 8). Also, varying

Table 2 Optimization of reaction conditions[a]

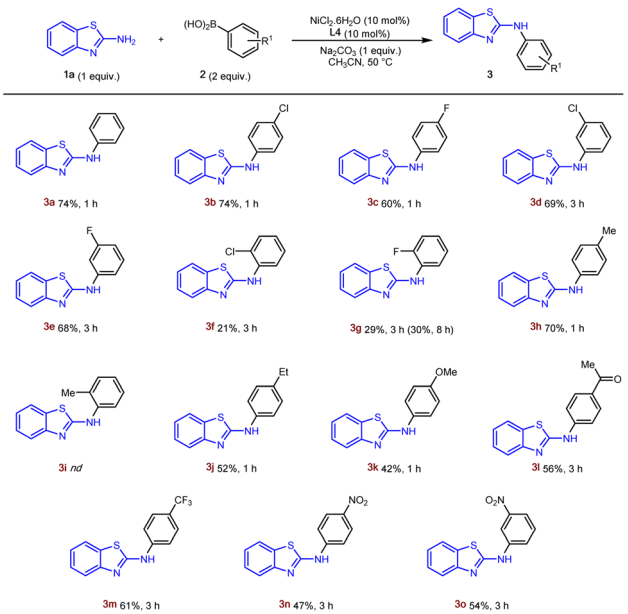
| Entry | $NiCl_2 \cdot 6H_2O$ (x mol%) | **L4** (y mol%) | Temperature (°C) | Time (h) | Yield (%)[b] |
|---|---|---|---|---|---|
| 1 | 20 | 20 | 60 | 8 | 71 |
| 2 | 20 | 20 | 70 | 8 | 56 |
| 3 | 20 | 20 | 50 | 8 | 72 |
| 4 | 20 | 20 | 50 | 12 | 66 |
| 5 | 20 | 20 | 50 | 4 | 75 |
| 6 | 20 | 20 | 50 | 1 | 72 |
| 7 | 10 | 10 | 50 | 1 | 72 |
| 8 | 5 | 5 | 50 | 1 | 65 |
| 9 | 10 | 10 | 50 | 1 | 52[c] |
| 10 | 10 | 10 | 50 | 1 | traces[d] |
| **11** | **10** | **10** | **50** | **1** | **74**[e] |
| 12 | 10 | 10 | 50 | 1 | 60[f] |

[a] Reaction conditions: **1a** (0.3 mmol), **2a** (0.6 mmol), $NiCl_2 \cdot 6H_2O$ (*x* mol%), **L4** (*y* mol%), $Na_2CO_3$ (2 equiv.), $CH_3CN$ (2 mL). [b] Isolated yield. [c] Under $O_2$ atmosphere. [d] Under $N_2$ atmosphere. [e] 1 equiv. of $Na_2CO_3$ was used. [f] 1.5 equiv. of **2a** was used.

the catalyst-to-ligand ratio from 1 : 1 to 1 : 2 or 2 : 1 proved unfavourable (SI, Table 3.6).

Moreover, we identified that 1 equivalent of base was adequate for the reaction (Table 2, entry 11). A reaction was carried out under pure $O_2$ atmosphere, however no improvement in yield was obtained (Table 2, entry 9). Likewise, the reaction under $N_2$ afforded only traces of the product indicating the role of an oxidative atmosphere in this transformation (Table 2, entry 10). Decreasing the equivalents of boronic acid **2a** to 1.5 equivalents lowered the yield to 60%, implying the need of 2 equivalents of **2a** to effect better conversion (Table 2, entry 12). We chose the reaction conditions shown in entry 11 (Table 2) as the optimal conditions for the Ni-catalyzed *N*-arylation of 2-aminobenzothiazoles **1**.

With the optimized conditions in hand, the generality of the developed method was studied. The scope of differently substituted aryl boronic acids in the C–N coupling of **1a** were studied (Scheme 2).



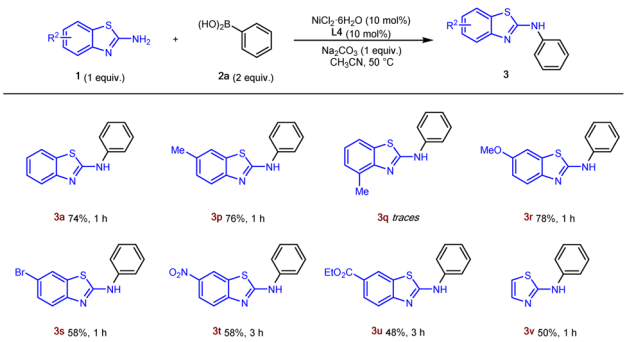

Scheme 2 Substrate scope of phenyl boronic acids.

The reaction accommodated a range of phenyl boronic acids with electron-rich or electron-deficient substituents in the *para*-, *meta*- and *ortho*-positions. It was noted that with halogenated (fluoro, chloro) phenyl boronic acids, *para*- and *meta*-substituted substrates underwent successful coupling in shorter time with an improved yield when compared to *ortho*-substituted derivatives (**3b–3g**). Also, a further increase in reaction time to 8 h didn't improve the yield in *ortho*-derivatives (**3f**, **3g**).

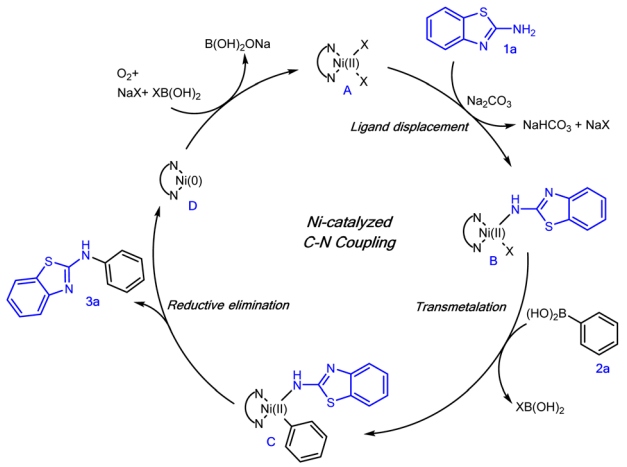
While 4-tolyl boronic acid afforded the corresponding product **3h** in good yield of 70%, the expected product was not formed with 2-tolyl boronic acid, possibly due to the steric effect of the *ortho*-methyl group. 4-Ethyl and 4-methoxy phenyl boronic acids gave the reaction in moderate yields (**3j**, **3k**). Electron-withdrawing groups ($-NO_2$, $-CF_3$, $-C(O)CH_3$) on **2** reduced the reaction rate in comparison to electron-rich derivatives, and afforded moderate yields of desired products (**3l**, **3m**, **3n**, **3o**, 47–61%).

The scope of electronically diverse 2-aminobenzothiazoles was also studied (Scheme 3). Relatively, 2-aminobenzothiazoles **1** with electron-rich substituents *viz.* methyl and methoxy at the 6th position showed quick reactivity with good yields of 76% and 78%, respectively. However, the presence of methyl group at the 4th position of 2-aminobenzothiazole seriously hampered the reactivity, providing only traces of product **3q** (confirmed by GCMS analysis). 2-Aminobenzothiazoles with electron-withdrawing groups ($-NO_2$, $-CO_2Et$) reacted smoothly to give **3t** and **3u**, but required an extended reaction time of 3 h for acceptable yields. 2-Amino-6-bromobenzothiazole can be converted into the corresponding coupled product **3s** in 58% yield in 1 h. To our delight, 2-aminothiazole reacted well under the optimized conditions and the expected product **3v** was formed in 50% yield.

Based on the analysis of previously reported Chan–Lam couplings and experimental observations,[9,26] we proposed a plausible mechanism for the aforementioned reaction, and is presented in Scheme 4.




Scheme 3 Substrate scope of 2-aminobenzothiazoles.




Scheme 4 Mechanism proposed for the Ni-catalyzed Chan–Lam coupling of 2-aminobenzothiazole **1a** with phenyl boronic acid **2a**.

The reaction was proposed to proceed in a catalytic cycle involving a sequence of ligand displacement, transmetalation, and reductive elimination. Initially, the coordination of amine **1a** with Ni(II) complex **A** results in the formation of Ni(II) complex **B** upon ligand displacement. Here, this ligand exchange occurs in the presence of a base that enhances the formation of **B**. The complex **B** participates in transmetalation with phenylboronic acid **2a** to form Ni(II) complex **C**. Then, the reductive elimination of **C** produced the desired product **3a** and Ni (0) species **D**. Finally, the complex **D** is re-oxidized to Ni(II) complex **A** in the presence of $O_2$ present in air. The aerobic regeneration of the catalyst is validated by a control experiment under nitrogen atmosphere providing only trace amounts of product.

## Conclusions

In summary, we have put forward an efficient and facile Ni-catalyzed Chan–Lam coupling of 2-aminobenzothiazoles and phenyl boronic acids to form the C–N coupled products in a shorter reaction time. This presents a novel entry to the heterocyclic amine substrates explored so far under Ni-catalyzed Chan–Lam protocols. The reaction afforded moderate to good yields of diverse *N*-arylated 2-aminobenzothiazoles, tolerating a range of functional groups. This 'open-flask' chemistry featuring mild and easy-to-handle reaction conditions proved a very attractive tool for the direct synthesis of *N*-arylated 2-aminobenzothiazoles.

## Conflicts of interest

"There are no conflicts to declare".

## Data availability

The data supporting this article have been included as part of the supplementary information (SI). Supplementary information: experimental procedures and spectral data ($^1$H and $^{13}$C NMR) of all compounds. See DOI: **https://doi.org/10.1039/d5ra06530e**.

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